USE FOR DEFERIPRONE

This Application is a National Phase Entry Application of PCT claiming priority from Application No. PCT/CA01/00956 filed Jun. 28, 2001.

FIELD OF INVENTION

The invention relates to the use of deferiprone for the prevention/stabilization/reduction of the risk of heart disease, such as heart failure, in patients having an iron overload condition such as is found in those suffering from for example, thalassemia, hemochromatosis, and myelodysplasia, and corresponding methods of treatment involving deferiprone therefor.

BACKGROUND OF THE INVENTION

Although reference is made in the following discussion to thalassemia specifically, the invention is not intended to be interpreted as limited only to the treatment thereof. Any chronic iron overload condition would benefit from treatment by utilizing the method described herein as well as the other aspects of the invention. For example, those suffering from hemochromatosis and transfused sickle cell anemia would also benefit.

Thalassemia, among other afflictions, must be treated by regular transfusions of red blood cells in order to extend the life of the patient. However, transfusions create a widespread iron overload in the patient. Iron overload is dangerous since the excessive iron can cause toxic degenerative changes in the heart, liver and endocrine organs.

While blood transfusions constitute the major source of increased iron load, having about 1 mg of iron per ml of transfused red blood cells, increased iron absorption from the gastrointestinal tract can be observed in some diseases and also cause iron overload. Typically, only 1 mg of the dietary iron is absorbed per day. However, some conditions such as thalassemia, dyserythropoietic anemias, sideroblastic anemias, and hereditary hemochromatosis are associated with increased absorption of dietary iron. However, only 1 mg of iron is lost each day through sloughing of cells from skin and mucosal surfaces and the body does not have any organ that can perform the role of regulating the iron excretion in conditions of iron overload. Consequently, increased dietary iron absorption can also lead to iron overload and iron-induced organ toxicity, the most serious of which is heart damage. Thus, even without blood transfusions, conditions such as thalassemia, or hemochromatosis lead to increased body levels of iron, resulting in iron toxicity and eventually heart damage.

Iron chelators are drugs that enhance the iron excretion. Iron overload is most often treated by the use of the iron chelator desferrioxamine. However, because desferrioxamine is not effective when given orally, it has to be given by a parenteral route. To be clinically effective, relatively large amounts of desferrioxamine are required to be infused daily for 8 to 12 hours and this regime has to be maintained for the life span of these patients. Due to the obvious difficulties associated with such a regime, an extensive amount of research has been directed towards the development of alternative iron chelators.

Recently another iron chelator, deferiprone by oral administration, has been used successfully for removal of iron in thalassemia patients who could not comply with desferrioxamine. While patient compliance is greater with deferiprone, it is not more effective than desferrioxamine in generally removing iron from the body. In some patients deferiprone is known to produce agranulocytoisis, which is a sudden decline in white blood cells in the body. Therefore, deferiprone has been approved in Europe for use in patients with thalassemia major for whom desferrioxamine is contraindicated or who demonstrate serious toxicity concerns with desferrioxamine therapy. According to regulatory bodies, desferrioxamine is currently the agent of choice.

Children who have untreated thalassemia generally die in the first decade of life from anemia and septicemia. When palliative transfusions are introduced, children live into their late teens, but eventually succumb to heart failure if iron overload is not treated. With the introduction of frequent chronic transfusion therapy and the use of subcutaneous desferrioxamine, most children are now surviving into adulthood. However, many still die before 30 years of age, most from heart failure.

Since there is no question that desferrioxamine can eliminate iron from the body, thus reducing the total body iron load, there are 2 possible reasons why there remains a high level of premature cardiac deaths in desferrioxamine treated patients: one is that patients do not take adequate amounts of the injectable chelator, and the other is that, while it removes iron from the liver and possibly the blood, its effect on the heart are secondary, not specific for this organ.

The number of patients who are compliant, with this therapy is limited since the use of desferrioxamine normally requires the use of an infusion pump for 8 to 12 hours, 5–7 days a week as long as patients continue to receive regular blood transfusions. This is a rigorous and uncomfortable treatment regime and many patients cannot or will not comply, which results in an increased iron load and iron toxicity in various organs, including the heart.

However, it is apparent that this is not, the only reason that thalassemia patients receiving desferrioxamine therapy develop iron-induced heart disease. Three separate techniques are generally employed in the assessment of iron overload: measurement of serum ferritin concentrations; measurement of hepatic iron concentrations by chemical means following a liver biopsy; and assessment of iron concentrations in the liver or heart or other organs by physical devices, such as SQUID (super quantum interference device) and MRI (magnetic imaging resonance). The lack of adequate compliance with injectable desferrioxamine leads to a generalized increased iron overload as revealed by increases in iron concentrations assessed by the above methods, and thus also to increased levels of iron in the heart. However, data now reveal that iron-induced heart disease occurs even in patients who are compliant with desferrioxamine, and even some of those who do not have high levels of total body iron as assessed by serum ferritin or liver iron concentrations. It has thus become evident that lowering of the total body iron alone is insufficient to protect against iron-induced heart damage.

There exists therefore a long felt need to improve the life expectancy of those patients who normally develop an iron overload condition, for example thalassemia patients, who are at risk of developing or who have developed cardiac disease, and to delay the onset of heart failure in the patient as long as possible. This need also applies to others suffering from conditions of chronic iron overload to for example those secondary to blood transfusions or those associated with increased dietary iron absorption. Applicant is aware of the following technical literature which discusses the clinical use of chelating agents in conditions of chronic iron overload. These references are referred to in the detailed description of the invention.